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Fetal Alcohol Syndrome: Craniofacial and Central Nervous System Manifestations

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Magnetic resonance imaging (MRI) is undertaken on fetal alcohol syndrome (FAS) subjects to document central nervous system (CNS) anomalies. The abnormalities found include agenesis and hypoplasia of the corpus callosum, cavum septi pellucidi, cavum vergae, ventriculomegaly, hypoplasia of inferior olivary eminences, small brain stem, and micrencephaly. Craniofacial anomalies range from the well-recognized FAS physiognomy to the more severe frontonasal "dysplasia" (median cleft face). CNS and craniofacial abnormalities are predominantly symmetric and central or midline. The association of these anomalies becomes self-evident with recognition of the concept of the midline as a special developmental field, vulnerable to adverse factors during embryogenesis and fetal growth and development. © 1996 Wiley-Liss, Inc.

KEY WORDS: MRI, agenesis of the corpus callosum, cavum septi pellucidi, cavum vergae, median cleft face, frontonasal dysplasia, midline developmental field defect

INTRODUCTION

The adverse effect to the fetus of prenatal alcohol exposure has been long known, but not widely recognized. It was forged into the public consciousness with the use of the term *fetal alcohol syndrome* (FAS) by Jones and Smith [1973]. These adverse effects became a clinically recognizable syndrome. It quickly became apparent that FAS is a major cause of physical and mental disability, as well as a significant load on the school and health systems and a burden to society. Numerous epidemiologic, clinical, psychological, and embryologic studies have described efforts to assess the scope of the problem. We attempt to define the range of central nervous system (CNS) manifestations in FAS, using magnetic resonance imaging (MRI) and to correlate these with craniofacial features and clinical findings. The latest innovations in neuroimaging, including advances in computer software, allow more accurate assessment of soft-tissue abnormality in FAS.

PATIENTS AND METHODS

Patients were chosen who met the criteria for FAS as defined by the Fetal Alcohol Study Group of the Research Society on Alcoholism [Sokol and Clarren, 1989]. These criteria include abnormalities in each of three categories: 1) prenatal and/or postnatal growth retardation, i.e., weight and/or length below the 10th centile; 2) central nervous system involvement, i.e., developmental delay, behavioral dysfunction, intellectual impairment and/or structural abnormalities, and microcephaly (occipito frontal circumference (OFC) below the 3rd centile), on imaging studies or autopsy; and 3) characteristic face, i.e., short palpebral fissures, elongated midface, long upper lip, flat philtrum, and thin vermilion border of upper lip.

MRI studies were done with a 1.5 tesla General Electric Signa system at Sioux Valley Hospital (Sioux Falls, SD). The scanner is equipped with *spoiled* GRASS (gradient recall acquisition in steady state) software which can obtain contiguous slices of varying thickness through the entire brain. The MR images were processed with BRAINS (brain research: analysis of images, networks, and systems) software developed by the Image Processing Laboratory of the Mental Health Clinical Research Center at the University of Iowa, Iowa City, IA.

CLINICAL REPORTS

Patient 1

M.S.A. was initially seen at age 5 9/12 years, along with 2 half-sibs, to rule out FAS. She was 99 cm tall and weighed 14 kg (<3 SD). Head circumference (OFC) was

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46.5 cm (mean for 15 months). She had short palpebral fissures, wide-set eyes, thin lips, myopia, and astigmatism. She had camptodactyly, small nails on the fifth fingers, and a hemangioma on the left interscapular area. A psychologic evaluation at 4 9/12 years showed moderate mental retardation, and attention deficit hyperactivity disorder (ADHD). Based on the clinical findings, the history of maternal alcohol abuse, and her 2 younger FAS half-sibs, she was diagnosed as having FAS.

At age 8 years she remains small and microcephalic. She is in special education.

Patient 2

R.B. was initially seen at age 5 1/2 months for developmental delay and finger contractures. He weighed 6 kg (10th centile) and was 60.3 cm tall (<5th centile). OFC was 39 cm (<2nd centile). He appeared small and microcephalic, with narrow forehead, short palpebral fissures, ptosis, broad and low nasal bridge, smooth philtrum, thin upper lip, a simian line on the right hand, camptodactyly, mild hypospadias, and hemangiomas of the left hip and left knee. Chromosomes were normal. He was diagnosed as having FAS. MRI showed agenesis of the corpus callosum.

Pregnancy was complicated by intrauterine growth retardation and abnormal maternal liver function due to chronic alcoholism, requiring abstinence and follow-up as a high-risk pregnancy. His mother was 35 years old, gravida 5; she drank excessively during the first 5 months of pregnancy.

At age 3 11/12 years, he had a borderline range of cognitive ability, 40% delay in receptive and expressive language, 40% delay in gross motor skills, 34% delay in fine motor skills, and mild-to-moderate hearing loss, presumably from chronic otitis media.

At age 4 7/12 years, he is 95 cm tall and weighs 14.6 kg (mean for age 3 years). OFC is 47 cm (mean for age 1 year). Facial features are typical of FAS. Palpebral fissures are short (16 mm), and inner canthal distance is increased (28 mm). He has striking camptodactyly of all digits. He has short fifth fingers and toes with hypoplastic nails. He is in special education.

Patient 3

F.T.L. was initially seen at age 8 months because of bilateral cleft lip and palate. She was 65 cm tall (5th centile) and weighed 6 kg (mean for age 4 months), with an OFC of 39.5 cm (mean for age 3 months). She had short palpebral fissures, increased inner canthal distance, low nasal bridge, wide cleft of the lip and palate with a prominent premaxilla with a single tooth, asymmetric nares, and micrognathia. On the vertex was an area of alopecia, due to a congenital localized skin dysplasia. She had a hemangioma, short neck, and prominent pilonidal pit. Fingers were disproportionate in length, with camptodactyly of the third, fourth, and fifth digits. The fifth fingers were strikingly short, with short fifth metacarpals and hypoplastic terminal phalanges and dysplastic nails. Fifth toes were short with hypoplastic toenails. She had significant developmental delays. Chromosomes were normal. She was diagnosed as having FAS. She had cleft lip repair at age 9 months, and cleft palate repair and feeding gastrostomy at age 18 months. At age 6 years she had partial complex seizures and occasional grand mal seizures. She had an exploratory laparotomy at age 12 years for an acute abdomen, and was diagnosed as having Crohn's disease.

At age 14 years, she is 146 cm tall (mean for age 11 years), weighs 43.2 kg (20th centile), and has an OFC of 49 cm (mean for age 3 years). She has a diagnosis of ADHD, moderate-to-severe mental retardation, and seizure disorder. She has aggressive, self-abusive, oppositional and obsessive-compulsive behaviors. She is under psychiatric and neurologic care in a group home.

Patient 4

J.S.O. was initially seen at age 5 months to rule out FAS. He was 54 cm long (mean for age 1 month) and weighed 3.4 kg (mean for a newborn). He was microbrachycephalic with an OFC of 37 cm (mean for age 1 month). He had hirsutism, thick eyebrows with synophrys, short palpebral fissures, increased inner canthal distance, low nasal bridge, anteverted nares, smooth philtrum, thin lips, small chin, and narrow palate. He had bridged palmar creases, and camptodactyly with small nails on fifth fingers and toes. He had a hemangioma, pilonidal pit, and sternotomy scar. He was diagnosed as having FAS.

He had a large ventricular septal defect (VSD), small atrial septal defect (ASD), and congestive heart failure requiring surgical repair at age 14 days and a reexploration with aortotomy and closure of a small residual VSD soon after. At age 11 months he had a grand mal seizure, and borderline abnormal EEG. Computerized tomography (CT) scan showed hydrocephalus of the occipital and temporal poles. Visual-evoked potential (VEP) study showed visual input to the cortex with significant discrepancy in latencies between right and left eye. Brain stem auditory-evoked potential (BAEP) study results were markedly abnormal, with no waves even at high-amplitude (60–100 dB) stimulation. Hearing aids were not tolerated. Seizures responded to medication and ceased at age 2 years. He gradually developed arrhythmia and bradycardia from "sick sinus syndrome," requiring a pacemaker at age 3 9/12 years. By age 14 1/2 months, he had severe delays in cognitive and motor skills, equivalent to a 3 1/2–4-month level. At age 7 9/12 years, he was functionally at the 28-month level.

At age 9 9/12 years, he is 113 cm tall (mean for age 5 9/12 years) and weighs 16.8 kg (mean for age 4 9/12 years). OFC is 48.25 cm (mean for age 20 months). His face is long and narrow; nose is high and broad. He has short palpebral fissures, myopia and intermittent right exotropia, striking camptodactyly, and short fifth digits. He has profound bilateral neurosensory hearing loss. A review of CT scan films showed agenesis of the corpus callosum (Fig. 3a,b). MRI is contraindicated by the pacemaker.

Patient 5

R.M.H. was initially seen at age 4 years for cleft palate. His height was 83.8 cm (mean for age 19 months), weight 10 kg (mean for age 12 months), and

OFC 44 cm (mean for age 6½ months). He had ptosis, short palpebral fissures, flat philtrum, thin lips, small chin, cleft palate, and slight facial asymmetry. His neck was short and wide, with limited movement. The right shoulder was higher than the left. Testes were undescended. He had short, incurved fifth fingers and syndactyly of toes 2 and 3. There was a pilonidal pit over the coccyx, and hair on interscapular and low lumbar areas. Neck X-ray showed hemivertebrae at C7 with fusion of transverse processes. He was diagnosed as having FAS. He had palatal repair and pharyngeal flap by age 5 years.

His growth rate dropped from the 5th centile. At age 12$^{3}/_{12}$ years, height was 115 cm (mean for age 5$^{11}/_{12}$ years), weight 20.9 kg (mean for age 6$^{7}/_{12}$ years), and OFC 46.5 cm (mean for age 11 months). He had pectus excavatum. Endocrine studies were normal. At age 16 years he has mild-to-borderline mental retardation. He is pleasant and compliant.

Patient 6

J.M. was initially seen at age 8 months, because of minor anomalies and a diagnosis of FAS since birth. Her height was 43 cm, weight 5,690 g (5th centile), and OFC 41 cm (2nd centile). Anterior fontanelles extended down to the midforehead. She had hypertelorism, upslanting palpebral fissures, flat nasal bridge, flat philtrum, median cleft of the vermilion border of the lip, and thick midline frenulum between the upper lip and the alveolar ridge. She was diagnosed as having frontonasal "dysplasia" (median cleft face syndrome). CT with contrast, sleep EEG, BAEP, and VEP were normal.

During her first year she had three bouts of meningitis and four CT scans before she was found to have a basal nasal meningocoele. Coronal and sagittal reformatted CT images showed the midline anterior cranial fossa to be abnormally low relative to the orbital roof, with a bony defect of the sphenoid. A large meningocoele, contiguous with the suprasellar cistern, occupied the expected position of the sphenoid sinuses, posteromedial ethmoid sinuses, posterior nasal, and anterior nasopharynx (Fig. 3c). This was repaired at age 1 year with bifrontal craniotomy and intradural repair with fascia lata graft. The small bony defect (12 mm) was left unrepaired. At age 3 years she had a drop in growth rate. Endocrine studies were normal, and growth rebounded spontaneously. Her lip was repaired, with tissue from her thigh used to supplement the interrupted orbicularis muscle. Because of developmental delay since infancy she was diagnosed as having FAS.

At age 8 years, height is 121.5 cm (40th centile), weight 27.2 kg (20th centile), and OFC 49.5 cm (2nd centile). Inner canthal distance is 3.8 cm (+2 SD), interpupillary distance 6 cm (>97th centile), and outer canthal distance 9 cm (−1 SD). Palpebral fissures measure 2.3 cm (mean for age 1.5 years). She has mild mental retardation.

Patient 7

M.M.C. was initially seen at age 10$^{1}/_{12}$ years. His height was 131 cm, weight 24.5 kg, and OFC 51.5 cm (5th centile). His face was long and narrow with normal eyes, smooth lip and ill-defined philtrum, and borderline thin lips. He had short fifth fingers and abnormal, ill-defined creases on the palms and fingers. He had academic problems and was retained in the third grade twice. Along with a history of maternal alcohol abuse, he was diagnosed as having mild FAS.

Pregnancy was complicated by premature rupture of membranes at 20 weeks, and hospitalization to control premature labor, followed by amnionitis and delivery at 29 weeks. At age 3 years he had surgery for strabismus and a left inguinal hernia. At age 7 years, he was evaluated for growth delay and learning disability; no clinical problems were found. At age 8$^{5}/_{12}$ years, he had a verbal IQ of 69, performance IQ of 82, and a full-scale IQ of 74. He had learning disability in auditory processing and in written and expressive language.

At age 12$^{6}/_{12}$ years, height is 138 cm and weight 28 kg (2–3 SD below mean). OFC is 51.5 cm (5th centile). He is the least involved in this series of patients.

Patient 8

S.E.C. was initially seen at age 2 years because of hyperactivity. She had a diagnosis of FAS since birth. Her height was 79.5 cm (5th centile), weight 9.5 kg (mean for age 12 months), and OFC 44 cm (mean for age 8 months). She was brachycephalic and had short palpebral fissures, mild ptosis, ill-defined philtrum and cupid's bow, and short fifth fingers. Palm creases were abnormal. She had camptodactyly of the fourth and fifth toes. She showed delays in gross and fine motor skills and language.

Over time, she had a decrease in growth rate. At age 4 years, height was 93.3 cm (mean for age 18 months), and OFC was 45.5 cm (mean for age 13 months). She is receiving speech and language therapy, physical therapy, and early childhood services for borderline/mild mental retardation. She is on medication for hyperactivity.

Patient 9

R.B.L. was initially seen at age 8$^{6}/_{12}$ years for bilateral cleft lip and palate. He had striking telecanthus/hypertelorism with inner canthal distance of 4.5 cm (>97%) and outer canthal distance of 8.5 cm (−2 SD), and very short palpebral fissures. He had deep-set blue eyes and arched eyebrows. Frontal hairline was low with a widow's peak. He was normocephalic with height and weight appropriate for age. Chromosomes were normal. He was diagnosed as having a median cleft face anomaly.

Lip repair was done soon after birth, and palate repair at age 1 year. He was diagnosed as deaf at age 2$^{6}/_{12}$ years. He had profound hearing loss, with speech detection thresholds of 80–85 dB HL. He was a resident of the School for the Deaf (Sioux Falls, SD) through his mid teens. At age 13 years, formal speech and language testing was unscorable because of limited understanding of language concepts and directions. He lacked spontaneous speech and generally used sign language. His general developmental level was between age 2–3 years.

At age 10$^{6}/_{12}$ years, height was 5.15 cm (5th centile), weight 42 kg (90th centile), and OFC 55.5 cm (90th centile). Hypertelorism remained striking, inner canthal

distance was 4.8 cm, and outer canthal distance was 9 cm. Palpebral fissures measured 1.8 cm (mean for term newborn). He appeared esotropic because of no apparent medial sclerae. His nose was wide with depressed tip and short columella. He had repaired lip and palate, thin upper lip, and collapsed palatal arches, with the lateral incisors behind the medial incisors. His upper arms appeared short relative to forearms, with no carrying angle and distally placed thumbs. Over time, as maternal alcohol abuse and mental retardation became apparent, the diagnosis of FAS was made. He was last seen at age 14$^{6}/_{12}$ years. He is now 20 years old, and has been enlisted as part of this study. MRI is pending.

RESULTS AND DISCUSSION

The criteria for the diagnosis of FAS were proposed by Sokol and Clarren [1989], primarily to address the issue of comparability of results of clinical observa-

Fig. 1.

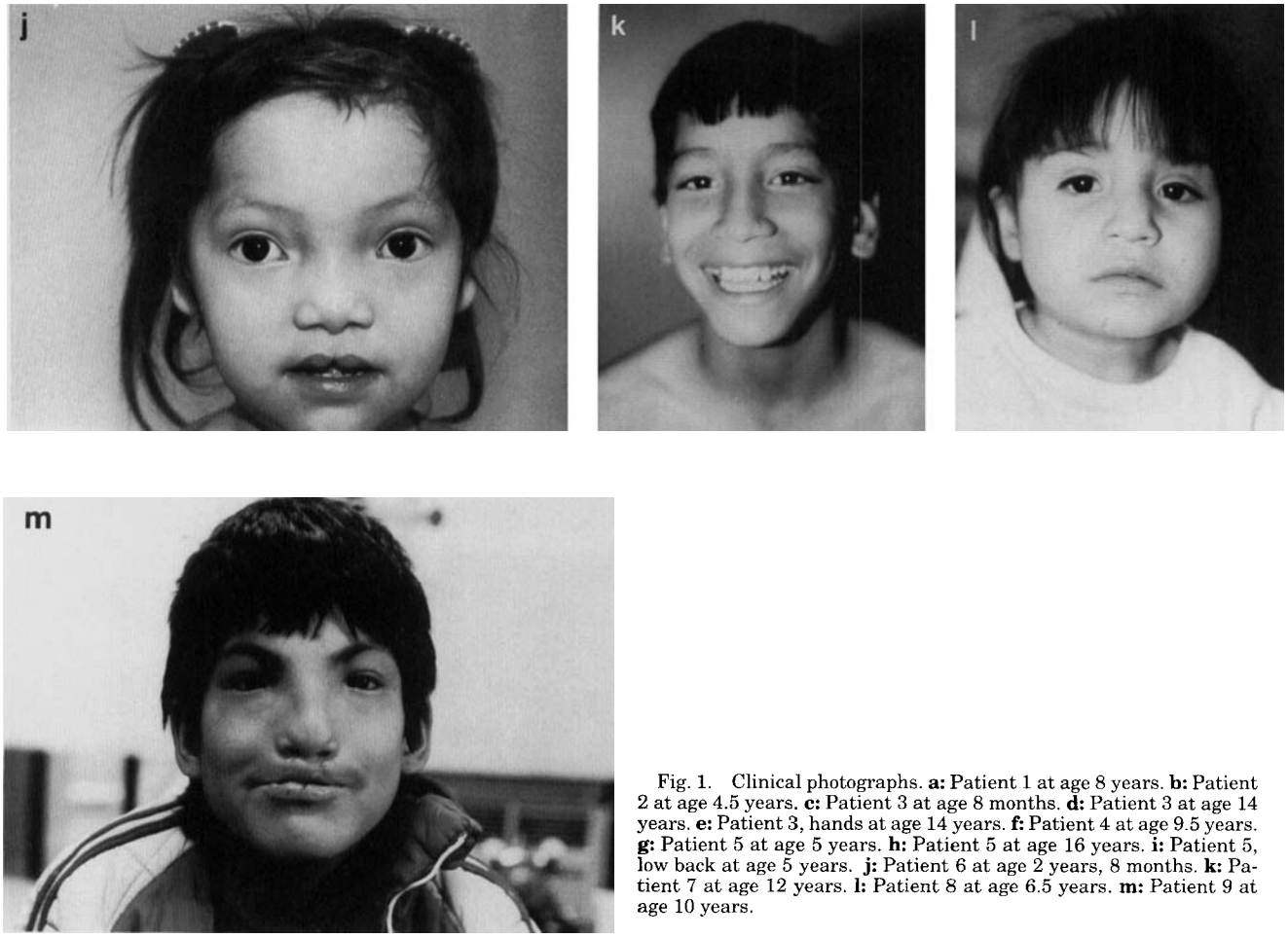


Fig. 1. Clinical photographs. **a:** Patient 1 at age 8 years. **b:** Patient 2 at age 4.5 years. **c:** Patient 3 at age 8 months. **d:** Patient 3 at age 14 years. **e:** Patient 3, hands at age 14 years. **f:** Patient 4 at age 9.5 years. **g:** Patient 5 at age 5 years. **h:** Patient 5 at age 16 years. **i:** Patient 5, low back at age 5 years. **j:** Patient 6 at age 2 years, 8 months. **k:** Patient 7 at age 12 years. **l:** Patient 8 at age 6.5 years. **m:** Patient 9 at age 10 years.

tions, scientific studies, and public health reporting. Limiting our patients to "classic" FAS cases limits our observations to the more severe end of the spectrum.

Figure 1a–m shows clinical photographs of patients 1–9. The patients range in age from 4.5–20 years. Patient 2 is Caucasian, and the rest are Native Americans. Although a number of these patients were suspected of having FAS at birth, they were often not referred for clinical genetics evaluation until infancy or early childhood when developmental delays became apparent. Quite commonly they were accompanied by foster parents or social workers, the patient having been removed from the home because of abuse and/or neglect. Maternal alcohol abuse was documented in all patients, either by the mother's admission of alcohol abuse during pregnancy or by medical and social service records of the mother's addictive behavior, intoxication during delivery, or admission to an alcohol treatment facility. Precise documentation of amounts and time of exposure was not possible. Even when the mother was available for interview, poor recall or outright denial were confounding factors.

A detailed accounting of maternal alcohol use during pregnancy can be useful in confirming or negating its role in causing a specific abnormality in a child; however, the amount/duration of maternal alcohol abuse and the clinical severity of fetal alcohol effects are not necessarily concordant. Both patients 2 and 7 had exposures only through the first 20 weeks of pregnancy. Patient 2 is more severely involved. His mother was a 35-year-old chronic alcoholic with abnormal liver function. Patient 7 is mildly affected. His mother was 19 years old, a younger alcoholic who was hospitalized, and therefore abstinent, after premature rupture of membranes. Maternal age, maternal health, degree of addiction, and a family history of other affected sibs are clinically relevant parameters that may have some predictive value when evaluating patients for FAS.

Reports have alluded to the tendency of the face to "normalize" with age [Spohr et al., 1993; Graham et al., 1988], making the diagnosis of FAS in an adult equivocal. Patient 3 is shown at ages 8 months and 14 years (Fig. 1c–e). Normally, the distance between the eyes is roughly equal to the width of an eye. By measuring the photographs, it becomes apparent that the eyes are not as far apart with age. Presumably the improvement is due to growth of the nasal bridge, pulling the inner canthi medially and decreasing the telecanthus. Patient 5 is shown at ages 5 years and 16 years (Fig. 1g–i). The upper lip does not appear as long with age. As the nose

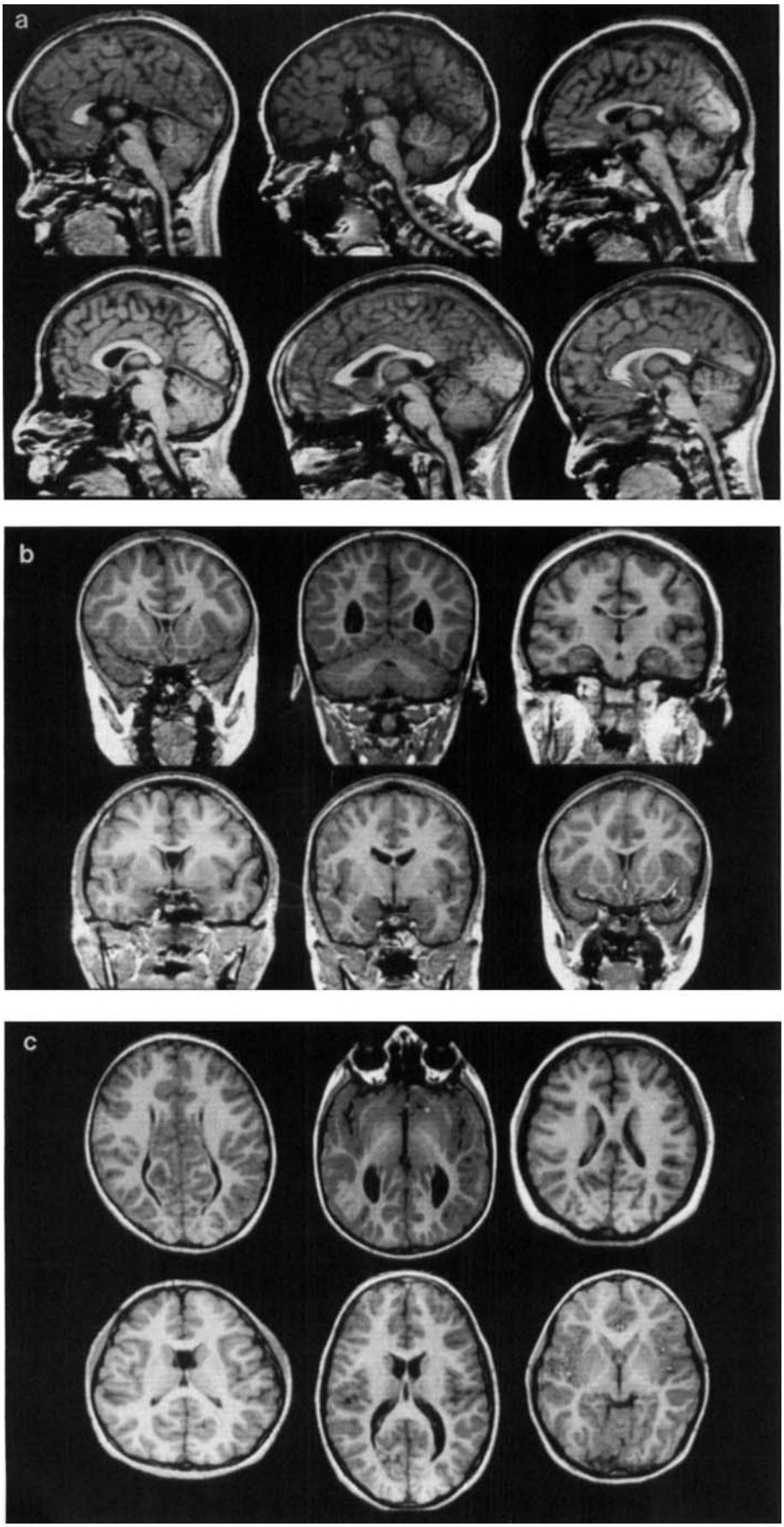


Fig. 2.

grows longer, the lip will appear shorter. Since the diagnosis of FAS is to a large extent based on overall appearance, the optimal time to assess for FAS is in infancy or early childhood, when facial appearance, growth retardation, and developmental delay are apparent, and when family and social histories are obtainable.

Associated manifestations include hand/foot/digit abnormalities, deafness, and hirsutism. Abnormal palmar and finger creases, and finger joint contractures, reflect abnormalities in underlying muscle, bone, and ligaments. Additionally, they reflect underlying CNS damage and loss of, or deficient, neuronal activity during development. In this series of patients, those with significant hand anomalies (patients 2–4) appear to be more severely affected physically and mentally. Limb development spans Carnegie stages 12–23 (26–57 days) [O'Rahilly and Müller, 1992], concurrent with eye, ear, and brain development. Thus, significant hand anomalies may have predictive value on CNS function. Deafness is severe in patients 4 and 9. Unfortunately, they do not have MRI studies to define anomalies in the brain stem, thalamus, and temporal lobes. Kotch and Sulik [1992b] show the otic anlagen to be extremely sensitive to ethanol exposure, including progenitors of neurons of the eighth cranial nerve and sensory cells of the inner ear. Hirsutism, a recognized manifestation in the newborn FAS patient, is often thought of as a transient feature. It is striking in patient 5 at ages 5 years and 16 years, especially in light of his Native American background.

The occurrence of major extracranial malformations in FAS is well recognized. Starting at stage 9 in the human embryo, the prechordal plate is merging with the cardiogenic plate [Müller and O'Rahilly, 1989], a likely explanation for the concurrent involvement of two separate but adjacent developmental fields. Patient 4 has agenesis of the corpus callosum and a large membranous ventricular septal defect, both anomalies occurring around 12–13 weeks of gestation, presumably in response to the same insult. The concurrence of these diverse anomalies is made understandable with knowledge of the spatial and temporal events in fetal development.

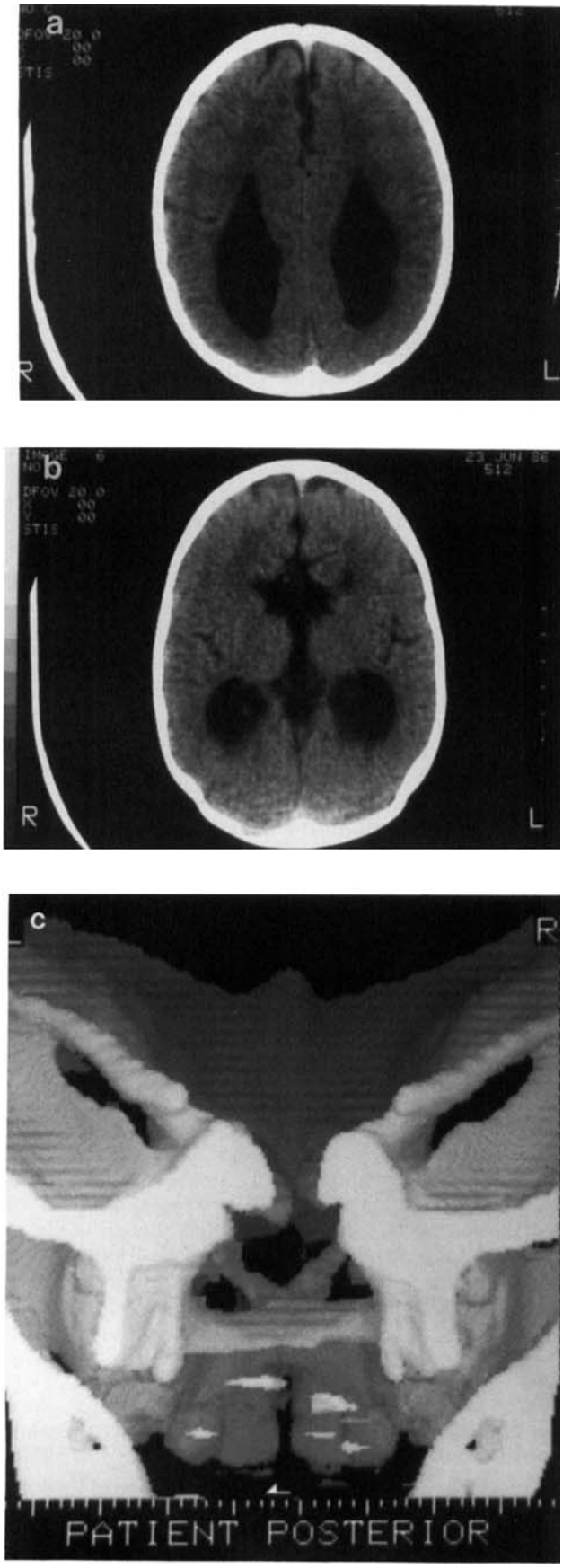
Types of CNS abnormalities include (Fig. 2): patient 1, partial agenesis of the corpus callosum, and cavum septi pellucidi; patient 2, almost complete agenesis of the corpus callosum, and mild micrencephaly; patient 3, hypoplastic corpus callosum, and micrencephaly; patient 4, agenesis of the corpus callosum; patient 5, cavum septi pellucidi, small cavum vergae, and micrencephaly; patient 6, basal nasal meningocoele; patient 7, disproportionately small brain stem, and hypoplasia of the inferior olivary eminences; and patient 8, no definitive abnormality apart from brain volume between 1–2 SD below the mean. The presence of a cardiac pacemaker precluded MRI studies on patient 4; however, prior axial CT scans showed agenesis of the corpus callosum (Fig. 3a,b). MRI was not done on patient 6 because of failed sedation, but prior CT scans showed a midline anterior cranial fossa defect (Fig. 3c). Scheduled twice, patient 9 failed appointments for MRI. All patients, except patients 7 and 9, had microcephaly (one of the criteria for inclusion). Microcephaly, for purposes of this study, refers to a head circumference below the 3rd centile. This usually shows up on MRI as a small brain or micrencephaly. Using recently published norms for whole brain volume by Andreasen et al. [1994], all patients had brain size more than 1–3 SD below control mean, except for patient 7. A striking characteristic of these patients is the OFC that lags far behind height and weight. This discrepancy appears to increase with age, as head growth plateaus and height continues to slowly increase.

The patients with agenesis of the corpus callosum (ACC) also had ventricular abnormalities (patients 1, 2, and 4). The lateral ventricles are further apart than usual because the gyrus cinguli, on the medial surface of the cerebral hemisphere located immediately above the corpus callosum, insinuates itself between the ventricles. In addition, the bundle of Probst (anteroposterior fiber tracts running between the frontal and the occipital lobes in each hemisphere) is prominent in the acallosal brain, presumably composed of fibers that would otherwise have crossed the midline as part of the corpus callosum. The third ventricle is often wider and rides higher than usual in the absence of the overlying corpus callosum. The posterior horns of the lateral ventricle are also commonly enlarged (colpocephaly) because of absence of the radiating fibers of the splenium of the corpus callosum, which normally form part of the walls of the occipital horns [Aicardi et al., 1987].

ACC was noted in patients 2 and 4, partial ACC in patient 1, and hypoplastic corpus callosum in patient 3. A review of ACC by Jeret et al. [1985] cited 33 cases in a series of 1,447 developmentally disabled individuals (2.3%). Although considered a rare abnormality with a general incidence of about 1 in 20,000 [Myrianthopoulos, 1987], ACC may prove to be more common with routine use of neuroimaging in FAS. Although hypoplastic corpus callosum (small but morphologically normal) is often considered a variant, Schaefer et al. [1991], in a study of 307 children, identified 23 with hypoplastic corpus callosum. They concluded that this is not a normal variant but rather an indicator of a more fundamental abnormality in brain development, based on correlates between morphometric and clinical findings.

The cavum septi pellucidi and cavum vergae are central structures bounded by the corpus callosum superiorly, and artificially separated by the vertical columns of the fornix. They are present in premature infants and are commonly closed in term infants. They are normally slit-like in adults. On neuroimaging they are usually considered variants. However, several cases have been described in association with hydrocephalus, or with previous meningitis [Shaw and Alvord, 1969], or as part of a spectrum of midline anomalies [Bodensteiner and Schaefer, 1990]. Considering the history of maternal alcohol use and other physical findings that support FAS, cavum septi pellucidi and cavum vergae

Fig. 2. Magnetic resonance images of (**a**) parasagittal, (**b**) coronal, and (**c**) axial sections of patients 1–3 (top), and 5, 7, and 8 (bottom), from left to right.



in these patients are presumed to be part of the clinical spectrum of FAS.

Patients 6 and 9, having strikingly wide-set eyes, were initially diagnosed as having a "median cleft face" (by V.P.J.) rather than FAS. Although there was a history of alcohol abuse during pregnancy, median cleft face was not recognized as part of FAS at the time. The interpupillary distance is increased in both patients, and hypertelorism is noted on CT scan in one (patient 6). Technically, telecanthus (increased distance between the inner canthi due to short palpebral fissures) is expected in FAS. As clearly described by Miller et al. [1981] in eye examinations of FAS patients, the short palpebral fissures cause the increase in medial canthal distance, i.e., primary telecanthus. It does not necessarily reflect an increase in distance between the bony orbits, i.e., hypertelorism and secondary telecanthus. Patient 9 also has very short palpebral fissures and cleft lip and palate. Patient 6 has a centrally cleft vermilion border of the upper lip and basal nasal meningocele.

Median cleft face (frontonasal "dysplasia") should be included in the clinical spectrum of FAS. Kotch and Sulik [1992a,b] describe a variety of facial and brain anomalies in mouse embryos exposed to ethanol in utero. These include exencephaly, arhinencephaly, pituitary "dysplasia," bilateral or unilateral cleft lip, maxillary hypoplasia, and median facial deficiencies and clefts. Pregnant mice were exposed to ethanol on gestational day 8, and the fetuses were examined on gestational days 11 or 14. Fetal abnormalities involving the midline included: exencephaly with a wide median cleft extending through forehead, nose, and upper lip; median cleft extending only through the upper lip; 2 cases with deficient frontonasal prominence derivatives and only one nostril; and 1 case with a midline cleft through the nose and the upper lip. These abnormalities mimic the frontonasal "dysplasia" spectrum in humans.

Apart from frontonasal dysplasia, holoprosencephaly should raise suspicion of in utero exposure to ethanol. A case of holoprosencephaly (V.P.J., personal communication) diagnosed by ultrasound in the third trimester, and with normal chromosomes on amniotic fluid cell culture (done to rule out trisomy 13), was found to be associated with maternal alcohol abuse. Ronen and Andrews [1991] reported on 3 patients with holoprosencephaly born to mothers who consumed alcohol only in the first trimester. One case with alobar holoprosencephaly had hypotelorism, flat nose, and median cleft lip, findings typical of holoprosencephaly. The other 2 patients with semilobar holoprosencephaly had a normal face, presumably because of a later discrete exposure affecting the forebrain but not the facial anlagen. Bonnemann and Meinecke [1990] reported on another case with cyclopia and agnathia, stillborn to a chronic alcoholic mother. In a review of holoprosencephaly, Muenke [1989] cites alcohol as one of the causative agents. Holoprosencephaly due to FAS is well-documented in mice

Fig. 3. **a,b:** CT scan of patient 4, showing ACC and dilated temporal and occipital horns (axial sections). **c:** CT scan of patient 6, showing bony defect in middle and posterior portions of the anterior cranial fossa (reformatted coronal sections).

[Sulik and Johnston, 1982]. A recent report describes holoprosencephaly in a fetal macaque monkey following prenatal exposure to ethanol [Siebert et al., 1991]. Since these patients do not have the facial anomalies typical of FAS, this cause-and-effect relationship may not be recognized. The occurrence of these more severe craniofacial anomalies should trigger inquiry into maternal alcohol use in pregnancy.

The relationship between midline facial abnormalities and underlying brain pathology was brought to clinical attention by DeMyer et al. [1964]. The holoprosencephaly spectrum is now recognized to include a single central incisor or premaxillary agenesis [Johnson, 1989], through the more severe ethmocephaly, cebocephaly, or cyclopia. Associated forebrain anomalies range from lobar to alobar holoprosencephaly. This is based on the interaction between the prechordal plate mesenchyme and the paraxial mesenchyme of the primitive node and the neural crest in the induction of face and forebrain development [Müller and O'Rahilly, 1989].

Table I lists critical phases of development of the brain and face, and provides a background for an understanding of brain and face anomalies. Arhinencephaly is restricted to absence of the olfactory bulbs and tracts. Holoprosencephaly, referring to a holospheric rather than a hemispheric forebrain, is more severe, and is based on disturbances in induction of the prosencephalon and other structures rostral, medial, and basal to it: anterior commissure, corpus callosum, septum pellucidum, olfactory and optic tracts, adenohypophysis, and face. Since fetal exposure to alcohol is episodic, and variable in duration, frequency, and dose, the effect on the rapidly evolving fetus will be highly random and variable in severity and in organs or tissues involved. Patients 1–5, who were more severely affected, had the most significant CNS abnormalities when compared with patients 7 and 8, who were less abnormal. The more facial anomalies and extracranial malformations present, the greater the likelihood of CNS anomalies. However, there appeared to be no pre-

TABLE I. Timing of Development of Selected Structures of Face and Brain Adversely Affected by Alcohol in the Human Embryo and Fetus*

	Anomaly	Gestational age (postovulatory weeks/days)	Carnegie embryonic stage	Crown-rump length (mm)
Cerebrum				
Mesenchyme of primitive node			6	
Eye				
Prechordal plate	Cyclopia	2.5/18	8	
Prechordal mesenchyme	Synophthalmia	3/20	9	
Optic primordium			10	
Nose				
Prechordal mesenchyme	Arhinia/proboscis	3/20	9	
Mesencephalic neural crest			10	
Forehead				
Mesencephalic neural crest				
Notochord	Skull anomalies[a]	3/22	10–11	
Forebrain				
Rhinencephalon, olfactory bulb, olfactory tubercle	Arhinencephaly	3/24	11	
Telencephalon	Holoprosencephaly	4/28	13	
Cerebral hemispheres			14	
Pharyngeal arches				
Neural crest			11–13	
Epipharyngeal plates			12–13	
Otic vesicle,otic capsule			11–14	
Cerebellum				
Cerebellar plate		4/28	13	4–5
Cerebellar hemispheres	hypoplasia	4/32	14	5–7
Cerebellar vermis		>8/	Early fetal	
Dentate nuclei		6/44	18	13–17
Medulla oblongata				
Inferior olivary nuclei	Hypoplasia[a]	>8/56–57	>23	23–33
Commissures				
Anterior commissure	Agenesis	10/	Early fetal	40
Hippocampal commissure	Agenesis	11/	Early fetal	
Corpus callosum[a]	Agenesis[a]	12/	Early fetal	45
Other				
Septum pellucidum	Cavum[a]	12–13		
Brain[a]	Micrencephaly[a]	Trimesters 1–3		

* References: commissures and cavum, Rakic and Yakolev [1968]; inferior olives and cerebellum, Müller and O'Rahilly [1990]; cerebellum and micrencephaly, Williams [1989]; face and forebrain, Müller and O'Rahilly [1989].
[a] Structural abnormalities found in our study.

cise concordance between a specific facial anomaly and a specific CNS anomaly, as one finds in the holoprosencephaly spectrum. This is understandable, since the upper face and the prosencephalon are adjoining structures, whereas the face and commissural plates (anterior commissure, and corpus callosum) are relatively more distant structures during embryogenesis.

Two striking characteristics of alcohol-induced CNS insult are symmetry and central or midline involvement. The symmetrical involvement is expected, considering the total "immersion" of the brain in alcohol, resulting in global micrencephaly and bilateral ventriculomegaly. Central and midline anomalies such as ACC contribute to the symmetry of the ventriculomegaly.

The occurrence of central or midline anomalies, such as ACC, cavum septi pellucidi, cavum vergae, holoprosencephaly, or median cleft face, is a reflection of the midline as a "weak seam," vulnerable to teratogenic agents or other adverse factors. The variety of midline malformations (neural tube defects, cardiac defects, omphalocele, gastroschisis, exstrophy of the bladder, and hypospadias) suggests vulnerability of the midline to adverse factors: teratogenic, genetic, chromosomal, and multifactorial. One can surmise that the vulnerability of the midline is due to problems in the process whereby adjoining developmental fields interphase. Developmental fields to the right or left of midline will need to interphase to establish the appropriate connections or associations needed to create the normal whole.

Opitz and Gilbert [1982] and Opitz [1985] have written on the concept of the midline as a developmental field. The central axis is critical in chordate development, with evagination or invagination resulting in lateral, ventral, and dorsal structures developing symmetrically from the midline or towards the midline. The midline should be considered a developmental field, i.e., "units of the embryo in which the development of complex structures appropriate to it is determined and controlled in a spatially coordinated, temporally synchronous, and epimorphically hierarchial manner" [Opitz, 1985]. An example of a developmental field would be the pronephros, mesonephros, and metanephros giving rise to the urinary tract or, closer to the subject at hand, the primitive node paraxial mesenchyme, the prechordal plate, and the neural crest mesenchyme as they interact to form the upper face and forebrain [Müller and O'Rahilly, 1989].

Recognition of the midline as a developmental field should lead to:

1. An understanding of the occurrence of a major midline anomaly in conjunction with normal lateral or paraxial structures, e.g., ACC as a solitary abnormality.
2. An understanding of the concurrence of several midline defects, and in some cases, secondary paraxial anomalies. ACC has been reported in association with holoprosencephaly, abnormal septum pellucidum, Dandy-Walker anomaly, pituitary abnormality, stenosis of the aqueduct of Sylvius, and colpocephaly [Aicardi et al., 1987].
3. An understanding of the interaction between different organs or systems, as adjacent developmental fields interact and influence one another, as with the holoprosencephaly spectrum and midline facial anomalies [Johnson, 1989].
4. An appreciation of mild malformations as part of a continuum between normal and abnormal. Instead of assuming mild malformations as incidental findings, a clinical reassessment could point to a significant anomaly. Absence of the septum pellucidum may point to a mild holoprosencephaly [Sarwar, 1989]. Enlarged posterior occipital horns may be due to agenesis of the splenium of the corpus callosum [Aicardi et al., 1987]. A wide cavum septi pellucidi may be associated with hypoplasia of the corpus callosum, hypoplasia of the optic nerve, growth failure, or seizures [Bodensteiner and Schaefer, 1990]. These conditions may be difficult to define on CT scans and should engender MRI studies.
5. An appreciation of (causal) heterogeneity of specific malformations. In response to different causes, a developmental field produces various grades of one anomaly. Holoprosencephaly can be due to chromosome abnormality, monogenetic disorders, diabetes, cytomegalovirus, toxoplasmosis, irradiation, quinine, salicylates, isotretinoin, phenytoin, and ethanol [Muenke, 1989; Ronen and Andrews, 1991].

Kotch and Sulik [1992b] demonstrated a dramatic increase in death of selected cell populations after ethanol exposure. Additionally, the teratogenicity of alcohol could also be ascribed to its CNS-depressant effect. By suppressing fetal consciousness/activity, it could impair activity-dependent neuronal development. Neuronal activity is important in effecting neuronal differentiation and maturation. Katz [1993], in a review of retinal and cortical development, cites a large body of evidence pointing to the need for neuronal activity (spontaneously generated or in response to the environment) in circuitry development. Neurons use this activity as a guide to the selection of synaptic partners. This is essential in creating a hierarchy of interacting neuronal units. The variable degree of CNS insult from ethanol exposure could cause readily apparent malformations or subtle changes in neuronal structure and function [Clarren et al., 1978; Peiffer et al., 1979; Wisniewski et al., 1983; Ferrer and Galofre, 1987; West et al., 1981; Miller and Robertson, 1993], which would later become apparent as behavioral or intellectual deficits.

In summary, a wide spectrum of craniofacial and CNS malformations exists in FAS. Similarly, mild or severe extracranial abnormalities are also highly varied. All of these are easily reconciled with a clear understanding of the temporal and synchronous changes in the morphogenetic developmental fields of the rapidly evolving embryo and fetus. Awareness of the wide range of ethanol teratogenicity stresses the importance of documenting major and minor malformations, both intracranially and extracranially. Establishing a diagnosis of FAS has a significant impact on plans to meet the medical, psychosocial, and educational needs of the child, and on the counseling and habilitation of the parents and family.

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